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ORIGINAL REPORT

SWOG S0809: A Phase II Intergroup Trial of Adjuvant Capecitabine and Gemcitabine Followed by Radiotherapy and Concurrent Capecitabine in Extrahepatic Cholangiocarcinoma and Gallbladder Carcinoma

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See accompanying editorial on page 2588; listen to the podcast by Dr Miksad at www.jco.org/podcasts

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ABSTRACT

Purpose
The role of postoperative therapy in extrahepatic cholangiocarcinoma (EHCC) or gallbladder carcinoma (GBCA) is unknown. S0809 was designed to estimate 2-year survival (overall and after R0 or R1 resection), pattern of relapse, and toxicity in patients treated with this adjuvant regimen.

Patients and Methods
Eligibility criteria included diagnosis of EHCC or GBCA after radical resection, stage pT2-4 or N+ or positive resection margins, M0, and performance status 0 to 1. Patients received four cycles of gemcitabine (1,000 mg/m^2 intravenously on days 1 and 8) and capecitabine (1,500 mg/m^2 per day on days 1 to 14) every 21 days followed by concurrent capecitabine (1,330 mg/m^2 per day) and radiotherapy (45 Gy to regional lymphatics; 54 to 59.4 Gy to tumor bed). With 80 evaluable patients, results would be promising if 2-year survival 95% CI were $>$ 45% and R0 and R1 survival estimates were $\geq$ 65% and 45%, respectively.

Results
A total of 79 eligible patients (R0, n = 54; R1, n = 25; EHCC, 68%; GBCA, 32%) were treated (86% completed). For all patients, 2-year survival was 65% (95% CI, 53% to 74%); it was 67% and 60% in R0 and R1 patients, respectively. Median overall survival was 35 months (R0, 34 months; R1, 35 months). Local, distant, and combined relapse occurred in 14, 24, and nine patients. Grade 3 and 4 adverse effects were observed in 52% and 11% of patients, respectively. The most common grade 3 to 4 adverse effects were neutropenia (44%), hand-foot syndrome (11%), diarrhea (8%), lymphopenia (8%), and leukopenia (6%). There was one death resulting from GI hemorrhage.

Conclusion
This combination was well tolerated, has promising efficacy, and provides clinicians with a well-supported regimen. Our trial establishes the feasibility of conducting national adjuvant trials in EHCC and GBCA and provides baseline data for planning future phase III trials.

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INTRODUCTION

Extrahepatic cholangiocarcinoma (EHCC) and gallbladder carcinoma (GBCA) are uncommon diseases, accounting for 10,650 new patient cases and 3,630 deaths in 2014 in the United States.[1] These entities are characterized by extensive locoregional infiltration and a high predilection for distant systemic spread.[2,3] Complete resection is the most effective and only potentially curative treatment,[2] but most patients present with locally advanced unresectable disease. Overall prognosis is poor, with only 5% to 19% of patients alive at 5 years.[4-6]

The role of chemotherapy or radiotherapy as adjuvant treatment after resection of EHCC or GBCA is unknown. Existing literature regarding postoperative treatment consists mostly of small single-institution retrospective reviews.[3-13] Furthermore, the pattern of failure after resection may be different, with local failure suggested as a prominent feature of EHCC but not of GBCA.[14] In EHCC, retrospective series have suggested, with few exceptions,[9,10] a benefit from radiotherapy or chemoradiotherapy. In GBCA, a recent nomogram suggested that chemoradiotherapy provides greater benefit than chemotherapy alone in all patient subsets.[15] In

contrast, a recent meta-analysis of clinical trials of biliary cancers concluded that the benefit of chemotherapy alone is greater than that of chemoradiotherapy, and radiotherapy alone is associated with no benefit.[16]

Given the paucity and poor quality of the data, we embarked on a phase II study of adjuvant chemotherapy and chemoradiotherapy in patients with resected EHCC or GBCA. The agents for this study—gemcitabine and capecitabine—were chosen based on single-agent activity[17,18] and nonoverlapping toxicities. The safety and efficacy of the combination have been demonstrated in a number of phase II trials, including SWOG (Southwest Oncology Group) 0202.[19-21] Capecitabine with radiotherapy to the upper abdomen is well tolerated and avoids the need for central venous catheterization and infusion pumps.[22-24] The primary goals of the study were to estimate survival and locoregional control rates associated with a modern adjuvant regimen and to establish a baseline for testing future regimens.

PATIENTS AND METHODS

Patients

The study was approved by the local institutional review boards, and informed consent was obtained from all participants. Eligibility criteria included pathologic diagnosis of EHCC or GBCA (but not ampullary cancer) after radical resection, with pathologic stage T2-4 or N1 or positive resection margins. Patients had to have recovered from surgery and have Zubrod performance status (PS) of 0 or 1. Computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis was required within 42 days before registration to rule out distant metastasis. Prior anticancer therapy for the current malignancy or upper abdominal radiotherapy at any time was not allowed. Patients had to have an absolute neutrophil count $>$ 1,500/mcl, platelets $>$ 100,000/mcl, serum creatinine $<$ 1.5 mg/dL, total bilirubin $<$ 1.5 $\times$ institutional upper limit of normal, and either AST or ALT $<$ 2.5 $\times$ institutional upper limit of normal. Patients had to be able to swallow medications, could not require tube feeding, and could not have intractable nausea or vomiting or any other condition that would interfere with absorption of oral medication.

Treatment

Treatment consisted of four cycles of chemotherapy with gemcitabine (1,000 mg/m^2 intravenously on days 1 and 8) and capecitabine (1,500 mg/m^2 per day on days 1 to 14, in divided doses twice daily) every 21 days. Dose adjustments of either or both agents were made based on toxicity experienced during preceding cycle. After reimaging, patients not experiencing progression went on to receive capecitabine (1,330 mg/m^2 per day, in divided doses twice daily, 7 days per week) concurrent with radiotherapy (45 Gy to regional lymph nodes [retropancreaticoduodenal, celiac, and portal vein nodes] and 54 to 59.4 Gy to preoperative tumor bed). Both three-dimensional planning and intensity-modulated radiotherapy (IMRT) were allowed. In patients receiving three-dimensional radiotherapy, total dose was 54 Gy in 30 fractions (59.4 Gy in 33 fractions for R1 resection at treating physician's discretion). In patients receiving IMRT, a concurrent boost was delivered for a total dose of 52.5 Gy in 25 fractions (55 Gy in 25 fractions for R1 resection at physician's discretion). Radiotherapy was delivered once daily, 5 days per week. Constraints for IMRT are summarized in Appendix Table A1 (online only). Clinical target volumes were based on review of preoperative scans, postoperative scans, markers placed by the surgeon, and surgery summary notes. Review of the targets with the surgeon was strongly recommended. Assessment of target motion at time of simulation and incorporation of this information into treatment planning were required.

After completion of protocol therapy, patients were seen in follow-up every 3 months, and CT or MRI of the chest, abdomen, and pelvis was obtained every 6 months for 2 years. Follow-up for survival continued to 5 years. Toxicity was scored using National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Quality Assurance

As part of this trial, we conducted a comprehensive central review of surgery, pathology, and radiotherapy plans. One slide from every block of the resection specimen had to be submitted, along with a copy of the pathology report and surgical notes. The purpose of this review was to confirm the diagnosis, site of origin, and pathologic stage of the tumor; verify the adequacy (radical resection) of the surgical procedure; and confirm margin status (R0 *v* R1).

Radiotherapy plans and copies of the preoperative and postoperative (prestudy) diagnostic imaging had to be submitted before initiation of therapy. The Quality Assurance Review Center (QARC) performed a rapid pretreatment review and an end-of-study review. The principal investigator performed a final review of all treatment plans in October 2013. To improve the uniformity of the treatment plans, guidance regarding contouring of targets and adjacent noninvolved organs (ie, organs at risk) and example plans were provided on the QARC Web site.[25]

Statistical Considerations

The primary goal of the trial was to estimate the stratum-specific (R0 and R1) and 2-year overall survival (OS) probabilities of patients treated with the prescribed regimen. The secondary goals were to estimate overall and stratum-specific disease-free survival (DFS), survival by anatomic subsite, probability of local relapse (LR), and frequency and severity of toxicity.

Review of published reports suggested a 2-year OS of 55% and 38% for R0 and R1 resections, respectively. We thus decided that results would be considered promising if the 95% CI for 2-year OS estimate excluded a rate $\leq$ 45% and if the stratum-specific point estimates were $\geq$ 65% for R0 and $\geq$ 45% for R1.

The target sample size of 80 evaluable patients was calculated to assure adequate precision of the 2-year stratum-specific survival probabilities. Given 35 patients within each stratum, 2-year survival probabilities and LR probabilities were estimated to be within $\pm$ 17%. Pooled 2-year OS, DFS, and LR probabilities could be estimated to within $\pm$ 12%.

Probabilities of OS and DFS were estimated using the Kaplan-Meier method. The probability of LR was summarized using a cumulative incidence estimate; death without LR was treated as a competing risk for LR. Statistical differences in event rates between groups according to primary disease site were assessed via log-rank test with stratification for resection margin. The strength of associations between treatment characteristics and incidence of LR were tested via Fisher's exact test.

RESULTS

Between December 1, 2008, and October 15, 2012, a total of 105 patients were registered. After central review, 21 patients were deemed ineligible: 13 by surgery review, three by pathology, and five by a combination of reasons. Five additional patients did not receive any protocol treatment: insurance coverage denial (n = 1), delay of treatment start past prespecified window because of infection (n = 1), withdrawal for personal reasons (n = 1), and unknown reasons (n = 2). The remaining 79 patients are included in this report.

Table 1 summarizes patient characteristics. Median age was 62 years. Primary disease site was bile duct in 54 patients (68%) and gallbladder in 25 patients (32%). Patients were stratified by resection margins: 54 had R0 and 25 had R1 resections. The majority of R0 patients (59%) had a PS of 0, whereas most R1 patients (72%) had a PS of 1. Table 2 summarizes pathologic stage as determined by central review using the American Joint Commission on Cancer staging manual (seventh edition).

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	R0 (n = 54) No.	R0 (n = 54) %	R1 (n = 25) No.	R1 (n = 25) %
Age, years				
Median	65.0		59.2	
Range	26.7 to 85.4		26.1 to 86.4	
Sex				
Male	24	44	14	56
Female	30	56	11	44
Hispanic				
Yes	4	7	1	4
No	49	91	17	68
Unknown	1	2	7	28
Race				
White	45	83	21	84
Black	5	9	2	8
Asian	4	7	0	0
Unknown	0	0	2	8
Primary disease site				
Bile duct	35	65	19	76
Gallbladder	19	35	6	24
Performance status				
0	32	59	7	28
1	22	41	18	72
Baseline laboratory values				
CEA, ng/mL	54		23	
Median	1.5		1.5	
Range	0.5 to 8.6		0.7 to 4.0	
CA19-9, U/mL	53		23	
Median	15.0		24.0	
Range	0 to 208.0		3.0 to 98.7	

Abbreviations: CA19-9, cancer antigen 19-9; CEA, carcinoembryonic antigen.

During chemotherapy, 60 patients (76%) had at least one dose modification or omission; these modifications and omissions were labeled as unplanned by the treating physician in 20 patients. Capecitabine was omitted for at least one cycle in four patients. Gemcitabine was omitted for at least 1 day per cycle in 18 patients. Among the 78 patients who received capecitabine, median total dose received per patient was 75,807 mg/m^2 (range, 1,366 to 97,111 mg/m^2). Median total dose of gemcitabine per patient was 6,967 mg/m^2 (range, 1,000 to 8,121 mg/m^2).

Table 2. Distribution of Pathologic Stage As Determined by Central Review

Stage	EHCC* Distal (n = 13) No.	EHCC* Distal (n = 13) %	EHCC* Hilar (n = 38) No.	EHCC* Hilar (n = 38) %	GBCA (n = 25) No.	GBCA (n = 25) %
IB	1	8	0	0	0	0
II	0	0	2	5	9	36
IIA	1	8	0	0	0	0
IIB	11	85	0	0	0	0
IIIA	0	0	7	18	6	24
IIIB	0	0	29	76	8	32
IV	0	0	0	0	2	8

Abbreviations: EHCC, extrahepatic cholangiocarcinoma; GBCA, gallbladder carcinoma.
*Three patients with EHCC had no central pathology review.

A total of 69 patients (87%) received radiotherapy (IMRT, 81%; three dimensional, 19%). Ten patients (EHCC, n = 8; GBCA, n = 2) did not receive radiotherapy (early progression, n = 5; personal reasons, n = 3; toxicity, n = 1; unknown reason, n = 1). Radiotherapy was delivered per protocol in 85% of patients. Median dose to R0 and R1 patients was 52.5Gy and 54Gy, respectively. Motion management (gating, tracking, or treatment at breath hold) was optional, and most patients (86%) were treated free breathing. Unscheduled interruptions during chemoradiotherapy occurred in 21 patients (radiotherapy and concurrent chemotherapy, n = 7; radiotherapy only, n = 1; chemotherapy only, n = 13).

Adverse effects included one death resulting from duodenal hemorrhage 5 months after therapy, which was possibly attributable to treatment. Nine additional patients experienced grade 4 toxicities, primarily hematologic: neutropenia (n = 7), leukopenia (n = 1), and ventricular tachycardia (n = 1). The most common grade 3 toxicities were neutropenia (35%), hand-foot syndrome (13%), diarrhea (8%), and lymphopenia (8%). A total of 68 patients (86%) completed treatment as planned; three patients discontinued therapy because of adverse effects.

With a median follow-up time of 35 months, 41 patients (52%) died. OS at 2 years was estimated to be 67% (95% CI, 52% to 78%) in the R0 group, 60% (95% CI, 38% to 76%) in the R1 group, and 65% (95% CI, 53% to 74%) overall (Fig 1). Median survival was 35 months overall, 34 months for R0, and 35 months for R1.

DFS at 2 years was estimated to be 54% (95% CI, 40% to 66%) in the R0 group, 48% (95% CI, 27% to 65%) in the R1 group, and 52% (95% CI, 40% to 62%) overall (Fig 2). Median DFS was approximately 26 months overall, 26 months for R0, and 23 months for R1.

A total of 14 patients developed LR, of whom nine experienced a concurrent distant relapse; 24 patients developed distant-only relapse. Table 3 summarizes first relapses by disease subsite. LR at 2 years was estimated to be 11% (95% CI, 4% to 18%) overall, 9% (95% CI, 2% to 17%) for R0, and 16% (95% CI, 2% to 30%) for R1. Three (30%) of the 10 patients who did not receive radiotherapy developed LR. Among the 69 patients who received radiotherapy, LR was significantly higher in patients who had a deviation from protocol (42% *v* 11%; $P = .02$).

Event rates were similar between patients according to primary disease site (Fig 3). Two-year OS was 68% (95% CI, 54% to 79%) for bile duct and 56% (95% CI, 35% to 73%) for gallbladder ($P = .87$). Two-year DFS was 54% (95% CI, 39% to 66%) for bile duct and 48% (95% CI, 28% to 66%) for gallbladder ($P = .71$). Two-year LR was 13% (95% CI, 4% to 22%) for bile duct and 8% (95% CI, 0% to 19%) for gallbladder ($P = .14$).

DISCUSSION

The main finding in this study is that gemcitabine and capecitabine followed by concurrent capecitabine and radiotherapy is an effective, tolerable, and promising adjuvant regimen in EHCC and GBCA. The 2-year OS of 65% (67% and 60% in R0 and R1, respectively) was significantly higher than the rates expected based on historical controls and exceeded our predetermined threshold for declaring success. Similarly, the low rates of local failure and the acceptable toxicity of this regimen are encouraging. We have also demonstrated the feasibility of accrual of patients with an uncommon diagnosis to a national

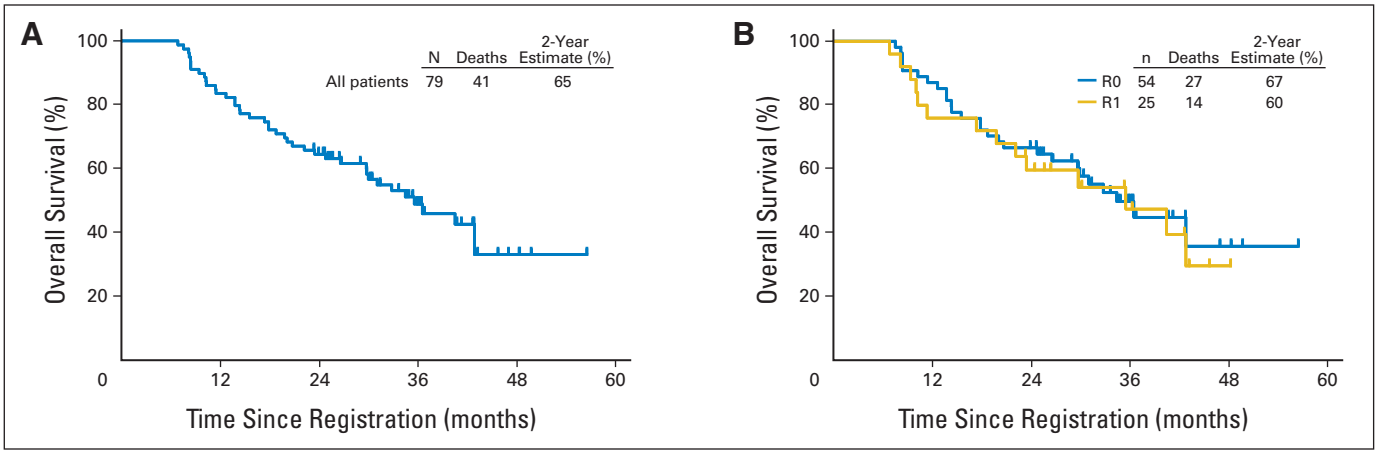

Fig 1. Overall survival (A) in all patients and (B) by resection margin; 2-year estimate was 65% for all, 67% for R0, and 60% for R1 patients (not significantly different).

clinical trial, an accomplishment that was not at all certain when we embarked on this phase II study.

The benefit of chemotherapy or radiotherapy as adjuvant treatment in resected EHCC or GBCA is unknown. Both entities are characterized by high rates of local infiltration, regional lymph node metastasis, and distant metastatic spread.[26,27] In a large series of 320 patients with EHCC who underwent radical resection, lymph node metastasis was found in 46%.[28] Similarly, in an analysis of specimens from super radical resections for GBCA, 24 (50%) of 48 patients had regional nodal spread, and in 16 (67%) of these, the involvement was in lymph node stations beyond those dissected in a radical cholecystectomy.[29] Consistent with these high rates of locoregional spread, published retrospective series on adjuvant radiotherapy or chemoradiotherapy[3-13] have suggested a locoregional relapse rate of 39% to 69%. One report suggested that locoregional recurrence is a prominent feature of EHCC (65% of first failures) but not of GBCA (28%)[14]; others did not find such a difference.[4] Existing literature regarding adjuvant treatment consists of single-institution reviews limited by heterogeneity of selection criteria and treatments.[3-13] The relative value of systemic therapy versus radiotherapy or chemoradiotherapy is also not clear. A meta-analysis of 20 studies showed a trend for improvement in OS with any adjuvant treatment (odds ratio, 0.74; $P = .06$). This improvement was statistically significant with adjuvant chemotherapy or chemoradiotherapy but not with radiotherapy alone. In contrast, a recent nomogram developed from the SEER-Medicare GBCA database suggests a survival advantage for ≥ T2 and node-positive patients and that chemoradiotherapy provides greater benefit than chemotherapy alone in all patient subsets.[15] This controversy is partly addressed by the current European phase III trials testing chemotherapy (capecitabine, gemcitabine plus oxaliplatin, and gemcitabine plus cisplatin) versus observation. In the United States, a phase III trial testing the value of chemoradiotherapy in addition to systemic chemotherapy is under development.

In patients with metastatic disease, fluorouracil, mitomycin, doxorubicin, and carmustine have shown some activity.[30] Newer drugs such as capecitabine and gemcitabine, alone[17,18] or combined with cisplatin[31,32] or oxaliplatin,[33] seem to be more effective. The combination of capecitabine and gemcitabine was chosen for our trial based on nonoverlapping toxicities and demonstrated safety and efficacy[19-21] in advanced biliary cancer. Capecitabine was chosen to be delivered concurrently with radiotherapy because it is well tolerated and avoids the need for central venous catheterization and infusion pumps during combined-modality therapy.[22-24] More recently, and long after accrual started to our trial, the combination of gemcitabine and cisplatin was shown to improve survival compared with gemcitabine alone, and it has become a standard in the metastatic setting.[32]

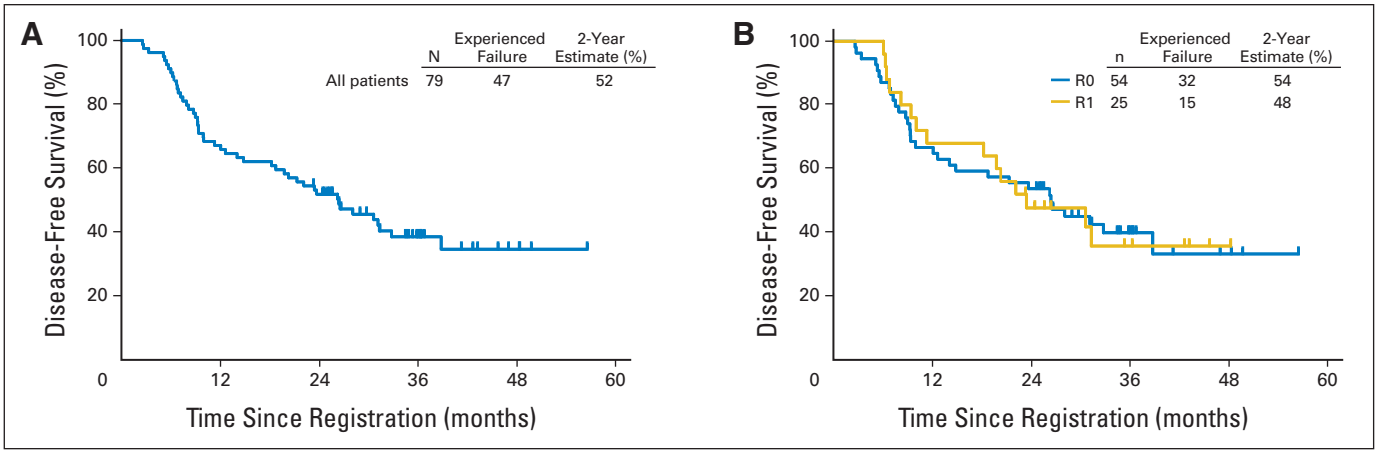

Fig 2. Disease-free survival (A) in all patients and (B) by resection margin; 2-year estimate was 52% for all, 54% for R0, and 48% for R1 patients (not significantly different).

Table 3. Pattern of First Relapse

	EHCC					
	Distal (n = 38)		Hilar (n = 13)		GBCA (n = 25)	
Recurrence	No.	%	No.	%	No.	%
Local only	3	8	1	8	0	0
Local plus distant	5	13	2	15	2	8
Distant only	11	29	1	8	11	44
Total	19	50	4	31	13	52

NOTE. Three patients for whom complete data were not available were excluded.
Abbreviations: EHCC, extrahepatic cholangiocarcinoma; GBCA, gallbladder carcinoma.

Because the combination of gemcitabine and cisplatin is not known to be superior to that of gemcitabine and capecitabine, we elected to complete the trial as designed.

A few important findings in this study relate to resection margins. First, the overall rate of R0 resection was quite high (68%), comparable to the best contemporary retrospective series.[34,35] One would have expected to find a lower rate of R0 resection in a national cooperative group trial. Second, OS and local control were similar in patients after R0 and R1 resections. This was an unexpected finding. Previous reports have consistently documented inferior outcomes after R1 resection in both EHCC[34,36] and GBCA.[35] The apparent improvement in outcomes in the R1 stratum may be cautiously interpreted as a sign of efficacy of the treatment regimen.

Another intriguing finding was that there was no difference in this study in pattern of failure between disease subsites. Although the literature on pattern of failure of biliary cancers is limited, it is widely accepted that local recurrence is a dominant feature of EHCC, with rates after curative resection ranging from 39% to 69%.[4,7,13] In contrast, the literature on GBCA is inconclusive in this regard. Some have reported a higher rate of distant metastasis in GBCA compared with EHCC,[14] but others have not found a difference.[4] In our trial, we observed that relapses (of any kind) tended to occur more rapidly (Fig 3) in GBCA, but at 2 years, the rates were essentially identical. The rate of local failure was low and nearly identical (10% and 13%) in disease subsites. It is impossible to determine whether this was a reflection of the biologic similarity of the two entities or a treatment effect, because all patients received radiotherapy.

An important feature of this trial was the guidance provided regarding delineation of targets and organs at risk and the series of comprehensive reviews taken to ensure quality. We performed central reviews of surgery, pathology, and radiotherapy plans to confirm diagnosis, site of origin, pathologic stage, adequacy of the surgical procedure, margin status, and adequacy of the radiotherapy plans. It has been demonstrated repeatedly that such quality measures are essential for the success of a clinical trial, particularly in one like this—the first ever to our knowledge in this clinical setting. These quality measures improve uniformity and reduce variability—arguably the greatest obstacles to detecting a signal of efficacy in a clinical trial. Indeed, of the total 105 patients registered, 21 (20%) were found ineligible. Furthermore, when a radiotherapy plan was found to deviate from protocol guidelines, LR was significantly higher (42% *v* 11%; $P = .02$). This is in agreement with findings in other trials and suggests, although does not prove, that nonadherence to protocol guidelines is detrimental.

A limitation of this study is the lack of a concurrent control arm. Recognizing that patients treated in prospective trials tend to have better outcomes than historical controls, a randomized design was considered. Ultimately, concerns regarding sample size, availability of patients with this rare disease, and consequently our ability to complete the trial in a timely fashion swayed us toward a single-arm design. Also, it should be noted that the results of this trial do not pertain to intrahepatic cholangiocarcinoma, which is an entity with different clinical features.

In summary, this was a positive phase II trial that met its stated goals. The results demonstrate the feasibility of conducting a national clinical trial in patients with this rare diagnosis and that gemcitabine and capecitabine followed by chemoradiotherapy with concurrent capecitabine is an effective and promising adjuvant regimen in EHCC and GBCA. In addition, we found that the rate of R0 resection was higher than expected in a national trial and that the tested chemoradiotherapy regimen produced high levels of local control. Also, surprisingly, the pattern of failure (distant *v* metastatic) in patients with EHCC was similar to that in patients with GBCA. The study provides data required for planning phase III trials in this setting and an adjuvant regimen for clinical use that is supported by current evidence.

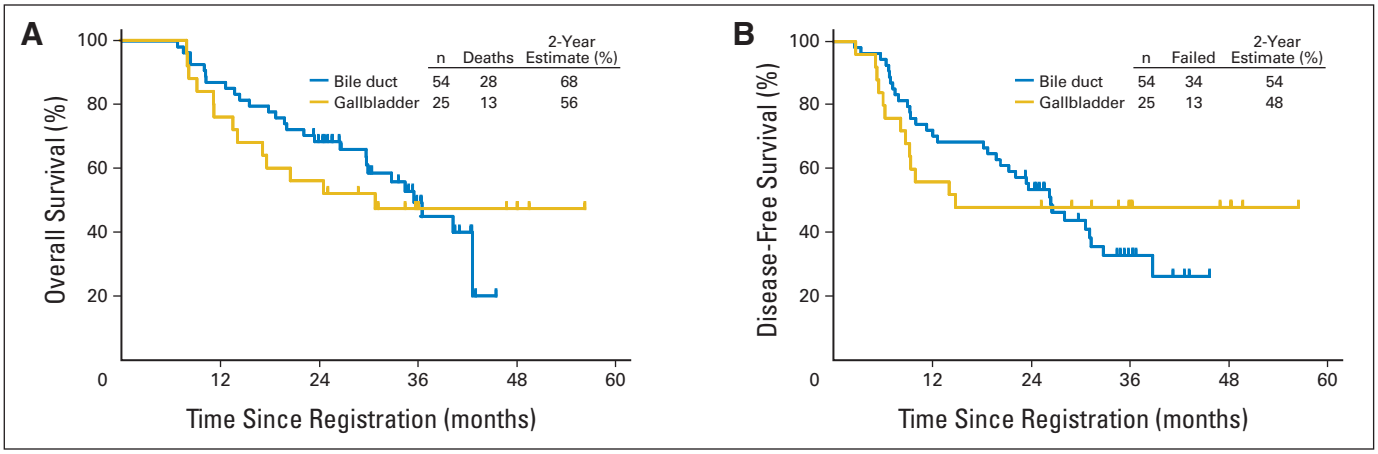

Fig 3. (A) Overall and (B) disease-free survival by primary site (no statistically significant differences between extrahepatic cholangiocarcinoma and gallbladder carcinoma).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Appendix

Table A1. IMRT Constraints

Structure	Constraint
Kidney (left and right)	Maximum dose ≤ 20 Gy; not > 10% of volume could be between 18 and 20 Gy
Liver	Mean dose < 30 Gy
Stomach/small intestine	Maximum dose ≤ 54 Gy; 2% of volume could be between 50 and 54 Gy; 25% of volume could be between 45 and 54 Gy
Spinal cord	Maximum dose ≤ 45 Gy
Duodenum	Maximum dose ≤ 54 Gy; not > 33% of volume could be between 45 and 54 Gy

Abbreviation: IMRT, intensity-modulated radiotherapy.